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(54) **PULVERISATEUR D'HYDROCORTISONE POUR ADMINISTRATION TOPIQUE**

(54) **CORTISONE SPRAY FOR TOPICAL ADMINISTRATION**

(57) L'invention concerne une préparation pharmaceutique d'application dermique d'hydrocortisone. Ce principe actif est dispersé par adjonction d'un ester d'acide gras partiel de sorbitanne de polyéthylène et d'autres auxiliaires tels que la lécithine et l'huile neutre. Ce système permet d'obtenir une suspension de particules de l'ordre du nanomètre du principe actif hydrocortisone liphophile.

(57) The present invention relates to a pharmaceutical mixture for the dermal application of hydrocortisone. The active agent is dispersed with the addition of a partial fatty acid ester of polyoxyethylene sorbitan and other auxiliaries like lecithin and neutral oil. This provides a suspension of nanoparticles of the lipophilic agent hydrocortisone.

# Cortisol Spray

The present invention relates to a pharmaceutical composition for the dermal application of hydrocortisone or a derivative thereof, a method for manufacture of this pharmaceutical composition as well as its application in therapy.

The body specific glucocorticoid hormone (cortisol), *Merck Index Eleventh Edition (1989) No. 4710, page 4711*, chemical description: 11, 17, 21-trihydroxy-pregn-4-en-3,20-dion, is dermally administered as an anti-inflammatory agent for treating inflammatory diseases, e.g. eczemas, psoriasis, dermatitis, contact allergies etc. The *Index Nominum 1992/93, Swiss Pharmaceutical Society, Medpharm, Scientific Publ. D-Stuttgart* lists for the active ingredient hydrocortisone 81 dermal preparations with registered trademarks. Of the derivatives, in particular the 21-acetate there are likewise known numerous preparations.

Since the mentioned inflammatory skin diseases can be resistant and protracted, a dermal preparation should be suitable for administering over a longer period of time. With the prolonged application of glucocorticoids on the skin in spite of a good effectiveness and provable healing successes, systemic effects and side effects are

problematic, for this see section G10 in *Rote Liste 1994, Arzneimittelverzeichnis des BPI (Bundesverband der Pharmazeutischen Industrie), ECV Editio Cantor, D-88322 Aulendorf*, No. 64009. Numerous dermal preparations therefore, instead of one of the highly effective new active ingredients of the glucocorticoid type described numerously in the literature, contain only the more weakly effective hydrocortisone which has been known for a long time and this even further in an extremely small dosage, e.g. mostly 1 mg per gram of formulation. One has therefore attempted to improve the lower effectiveness of such preparations by increasing the dosage. Preparations with a higher dosage even of hydrocortisone must however due to the known side effects and the numerous counter indications be subjected to medical control and mandatory prescription.

It is therefore the object of the invention to manufacture for the well-tried active ingredient hydrocortisone a dermal preparation with an improved effectiveness with a smaller dosage.
In the narrower sense, it is the object of the present invention to manufacture for the active ingredient hydrocortisone an improved dermal preparation which is suitable for releasing without prescription as a so-called OTC preparation (Over-the Counter preparation) within the framework of the so-called self-medication.

The achievement of the object is based on the consideration that by increasing the solubility of the active ingredient hydrocortisone in the formulation base, an improvement in effectiveness with an unchanged low concentration is to be achieved. Hydrocortisone itself is weakly soluble in water which in dermal formulations is a considerable constituent. The *Merck Index, loc, cit.*, indicates a water solubility of 0.28 mg/ml (25°C). In ethanol the active ingredient is more soluble: 15 mg/ml (25°C). The addition of large quantities of ethanol for improving the solubility of the active ingredient is not suitable for dermal preparation, since ethanol for other constituents of the formulation likewise acts as a solvent and encourages the drying of the skin. Alternatively to the application of an unsuitable solvent numerous publications suggest aqueous finely dispersed systems with dissolving properties based on lipid mixtures. Herein the insoluble active ingredient is enclosed in lipid particles with a particle size of less than 1 µm, which with the aqueous carrier fluid form a colloid-dispersed or finely dispersed system, which although does not represent an true molecular dispersed solution, is however sufficiently homogeneous for a dermal formulation. In the literature on the subject there is mentioned the encapsulation of lipophils and/or weakly soluble active ingredients in micelles, mixed micelles, reverse micelles, unilamellar or multilamellar liposomes, nanocapsules, nanoparticles etc.

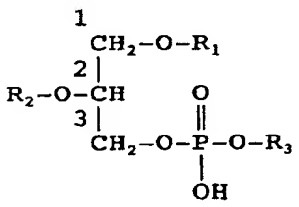
The document DE-A-4018995 describes the incorporation of corticosteroids into an amphiphillic, non-ionic lipid phase, which in an aqueous phase forms vesicles with a size of 10 to 5000 nm. The document WO-A-93/18752 describes compositions for the dermal application of pharmaceutical products with particles from an oily fluid, from an emulsifying agent, e.g. a phospholipid, and from a non-ionic tenside. The particles have a size of 50 to 500 nm which in the examples in the document are achieved by treatment in a homogeniser. For the oily fluid as well as for the emulsifying agent and the tenside in each case there are mentioned numerous possible substances in the document.

It has been surprisingly found out that a lipophile formulation base consisting of partial fatty acid ester of polyoxyethylene sorbitan, of a phospholipid and of a neutral oil is suitable for manufacturing a particularly homogeneous finely dispersed nanodispersion of the active ingredient hydrocortisone. The present invention has as the subject-matter a pharmaceutical composition for the dermal application of a corticoid, which has the following constituents:

a) the active ingredient 11, 17, 21 -trihydroxypregn-4-en-3,20-dion (hydrocortisone) or a derivative thereof, where appropriate in combination with a wound healing agent;

b) at least one partial fatty acid ester of polyoxyethylene sorbitan or a combination thereof;

c) at least one essentially pure phospholipid of the formula:

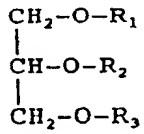


(I)

where $R_1$ indicates $C_{10-20}$-acyl, $R_2$ hydrogen or $C_{10-20}$-acyl, $R_3$ hydrogen, 2-trimethylamino-1-ethyl, 2-amino-1-ethyl, $C_{1-4}$-alkyl, $C_{1-5}$-alkyl substituted by carboxy, $C_{2-5}$-alkyl substi-

tuted by hydroxy, $C_{2-5}$-alkyl substituted by carboxy and hydroxy or $C_{2-5}$-alkyl substituted by carboxy and amino, the inositol or glyceryl group, or salts of these compounds;

d) a triglyceride of the formula:



(II)

where $R_1$, $R_2$ and $R_3$ indicates $C_{8-24}$-acyl;

e) water as a carrier fluid in the purity required for the transdermal application; and where appropriate

f) aiding agents suitable for dermal forms of administration.

This pharmaceutical composition is distinguished by favourable phase properties of the solubilised active ingredient. Thus with a present opalescence and transparency in counter light it is only to be recognised by an extremely slight milky murkiness that the suspension still has physical differences with respect to the ideal condition of a pure molecular solution. Electron microscope imaging shows that a population of more than 98% of the active ingredient is present in a Gaussian distribution as a dispersion of particles (nanoparticles) with a particle size of less than approx. 50 nm (nanodispersion).

These differences with respect to a pure solution are however acceptable on account of the particularly good homogeneity properties of the dispersion, which for example can be detected by a surprisingly high storage stability, e.g. no segregation after a storage lasting several months at temperatures of up to room temperature (the stability to be expected by extrapolation is longer than two years). All these properties may be achieved without the additional application of a homogeniser by way of a simple mixing of the constituents.

A preferred embodiment form concerns a pharmaceutical composition containing:

a) the active ingredient hydrocortisone or the 21-acetate, where appropriate in combination with dexpanthenol;
b) the composition consisting of polysorbate 20, 80 and 60;
c) purified lecithin from soya beans;
d) a triglyceride from the group of neutral oils; and
e) water as a carrier fluid in the purity required for the dermal application; and where appropriate
f) aiding agents suitable for dermal forms of administration.

The active ingredient hydrocortisone - component a) - in the pharmaceutical composition described nearer the beginning is contained in the dosage allowable

for the dermal application. In the commercial formulation according to the *Rote Liste or Arzneimittelkompendium der Schweiz, Documed Basel, Schweiz*, in prescription-free pre-

parations there is contained a dose of approx. 0.1 to 0.5% (calculated with respect to free hydrocortisone).

A derivative of hydrocortisone is in particular the 21-acetate, 21-acetate-17-propionate (aceponate), 21-bendazac, 17α-butyrate, 17α-butyrate-21-propionate, 21-cipionate (cyclopentane propionate), 21-disodium phosphate, 21-hydrogen succinate, 21-sodium succinate, 21-tebutate (tert. butyl acetate), 17-valerate or xanthogenate.

The active ingredient hydrocortisone or one of the mentioned derivatives may in the pharmaceutical composition be contained in combination with a known wound treating agent or epithilisation agent, e.g. dexpanthenol.

The component b) - partial fatty acid ester of polyoxyethylene sorbitan - consists preferably of an essentially pure or mixture of various esters of sorbitan, wherein the structure of the fatty acid groups and the length of the polyoxyethylene chains vary. The sorbitan is preferably ethered by three hydrophillic polyoxyethylene chains and estered by a hydrophobic fatty acid group. The sorbitan may however also be ethered only by one or two hydrophillic polyoxyethylene chains and accordingly estered by three or two hydrophobic fatty acid groups. In total the sorbitan base body is substituted by at least one to at most three hydrophillic polyoxyethylene groups

and accordingly by at most three and at least one hydrophobic fatty acid group.

The polyoxyethylene chain is straight-chained and comprises preferably 4-10, in particular 4-8, ethylene oxide units. The ester groups on the sorbitan base body are derived from a saturated or unsaturated, straight-chained carbon acid and an even number of 8-10 C-atoms. The ester group derived from this carbon acid is preferably straight chained with 12, 14, 16 and 18 C-atoms, e.g. n-dodecanoyl, n-tetradecanoyl, n-hexadecanoyl or n-octadecanoyl. The ester group derived from an unsaturated carbon acid with an even number of 8-20 C-atoms is preferably straight-chained with 12, 14, 16 and 18 C-atoms, e.g. oleoyl. The mentioned esters of sorbitan, fulfil the details mentioned in the British Pharmacy list (special monograph) or Ph. Helv. VII. There applies in particular the product descriptions published by the mentioned manufacturers with the details of data sheets for the product concerned, in particular specifications such as form, colour, HLB-value, viscosity, rising melting point and solubility.

Suitable partial fatty acid esters of polyoxyethylene sorbitan are commercially obtainable under the name Tween® of the company ICI and known under the chemical description polyoxyethylene (20 or 4)-sorbitan monolaurate (TWEEN 20 and 21), polyoxyethylene-(20)-sorbitan

monopalmitate or monostearate (TWEEN 40 and 60), polyoxyethylene-(4 or 20)-sorbitan-monostearate or tristearate (TWEEN 61 and 65), polyoxyethylene- (20 or 5)-sorbitan monooleate (TWEEN 80 or 81) or polyoxyethylene-(20)-sorbitan trioleate (TWEEN 85).

In a particularly preferred embodiment form of the invention one uses as component b) a combination consisting of TWEEN 20, TWEEN 80 and TWEEN 60, or polysorbate 20, 80 and 60.

The component b) is contained in the pharmaceutical composition in a quantity part of approx. 1.0% to 5.0%, preferably 1.0% to 3.0% (with respect to the total weight of
the formulation).

Component c) phospholipid of the formula I. The nomenclature of the phospholipid (I) and the numbering of the C-atoms is effected by way of the recommendations (sn-nomenclature, stereospecific numbering) cited in the Eur. J. of Biochem. 79, 11-21 (1977) of the IUPAC-IUB Commission on Biochemical Nomenclature (CBN).

$R_1$ and $R_2$ with the meanings $C_{10-20}$-acyl are preferably straight chained $C_{10-20}$-alkanoyl with an even number of C-atoms and straight-chained $C_{10-20}$ alkenoyl with a double bonding and an even number of C-atoms.

Straight chained $C_{10-20}$ alkanoyl $R_1$ and $R_2$ with an even number of C-atoms are for example n-dodecanoyl, n-tetradecanoyl, n-hexadecanoyl or n-octadecanoyl.

Straight chained $C_{10-20}$ alkanoyl $R_1$ and $R_2$ with a double bonding and an even number of C-atoms are for example 6-cis- or 6-trans-, 9-cis- or 9-trans-dodecenoyl, -tetradecenoyl, -hexadecenoyl, -octadecenoyl or -icosenoyl, in particular 9-cis-octadecenoyl (oleoyl), further 9,12-cis-octadecadienoyl or 9, 12, 15-cis-octadecatrienoyl.

A phospholipid (I), wherein $R_3$ indicates 2-trimethylamino-1-ethyl is described with the trivial name lecithin and a phospholipid (I), wherein $R_3$ indicates 2-amino-1-ethyl is described with the trivial name kephalin. Suitable for example are naturally occurring kephalin or lecithin, e.g. kephalin or lecithin from soya beans or chicken eggs with various or identical acyl groups $R_1$ and $R_2$, or mixtures thereof.

The phospholipid (I) may however also have a synthetic origin. Under the term synthetic phospholipid one defines phospholipids which with respect to $R_1$ and $R_2$ have a unitary composition. Such synthetic phospholipids are preferably the lecithins and kephalins defined previously, whose acyl groups $R_1$ and $R_2$ have a defined structure and are derived from a defined fatty acid with a

degree of purity of more than approx. 95%. $R_1$ and $R_2$ may be the same or different and unsaturated or saturated. Preferably $R_1$ is saturated, e.g. n-hexadecanoyl, and $R_2$ unsaturated, e.g. 9-cis-octadecenoyl (oleoyl).

The term "naturally occurring" phospholipid (I) defines phospholipids which with respect to $R_1$ and $R_2$ do not have a unitary composition. Such natural phospholipids are likewise lecithins and kephalins whose acyl groups $R_1$ and $R_2$ are structurally undefinable and are derived from naturally occurring fatty acid mixtures.

The requirement "essentially pure" phospholipid (I) defines a degree of purity of more than 90% (weight), preferably more than 95%, of the phospholipid (I), which can be proven by way of suitable methods of determination, e.g. paper chromatographically, with thin film chromatography, with HPLC or enzymatic colour test.

In a phospholipid (I) $R_3$ has the meaning $C_{1-4}$ alkyl for example methyl or ethyl. The meaning methyl is preferred.

$R_3$ with the meanings $C_{1-5}$-alkyl substituted by carboxy, $C_{2-5}$-alkyl substituted by hydroxy or $C_{2-5}$-alkyl substituted by carboxy or hydroxy are for example 2-hydroxyethyl, 2,3-dihydroxy-n-propyl, carboxymethyl, 1- or

2-carboxyethyl, dicarboxy-methyl, 2-carboxy-2-hydroxyethyl or 3-carboxy-2,3-dihydroxy-n-propyl.

$R_3$ with the meaning $C_{2-5}$-alkyl substituted by carboxy and amino is e.g. 3-amino-3-carboxy-n-propyl or 2-amino-2-carboxy-n-propyl, preferably 2-amino-2-carboxy-ethyl. Phospholipids (I) with these groups may be present in salt form, e.g. as sodium or potassium salt.

Phospholipids (I), wherein $R_3$ indicates the inositol or glyceryl group, are known under the descriptions phosphate idylinositol and polyphosphate idylglycerol.

For the acyl residuals in the phospholipids (I) as well as in the triglycerides (II) the descriptions indicated in brackets are usual:

9-cis-dodecenol (lauroleoyl), 9-cis-tetradecenoyl (myristoleoyl), 9-cis-hexadecenoyl (palmitoleoyl), 6-cis-octadecenoyl (petroseloyl), 6-trans-octadecenoyl (petroselaidoyl), 9-cis-octadecenoyl (oleoyl), 9-trans-octadecenoyl (elaidoyl), 9, 12-cis-octadecadienoyl (linoleoyl), 9,12,15-cis-octadecatrienoyl (linolenoyl), 11-cis-octadecenoyl (vaccenoyl), 9-cis-icosenoyl (gadoleoyl), 5,8,11,14-cis-eicosatetraenoyl (arachidonoyl), n-dodecanoyl (lauroyl), n-tetradecanoyl (myristoyl), n-hexadecanoyl (palmitoyl), n-octadecanoyl

(stearoyl), n-icosanoyl (arachidoyl), n-docosanoyl (behenoyl), n-tetracosanoyl (lignoceroyl).

A salt of the phospholipid (I) is preferably pharmaceutically acceptable. Salts are defined by the existence of salt forming groups in substituents $R_3$ as well as by the free hydroxy group of phosphorous. Likewise the formation of inner salts is also possible. Preferable are alkali metal salts, in particular sodium salts.

The component c) is added in a preferred concentration of approx 0.05 to 1.0% by weight, preferably 0.05 to 0.1% by weight with respect to the total weight of the formulation. In a particularly preferred embodiment form one uses a purified lecithin of soya beans of the quality LIPOID S 100.

Component d): in one of the triglycerides of the formula II used as component d) $R_1$, $R_2$, $R_3$ mean a straight-chained $C_{8-24}$-acyl with an even number of C-atoms, in particular n-octanoyl, n-dodecanoyl, n-tetradecanoyl, n-hexadecanoyl, n-octadecanoyl, 9-cis-dodecenoyl, 9-cis-tetradecenoyl, 9-cis-hexadecenoyl, 9-cis-octadecenoyl or 9-cis-icosenoyl. The meanings of $R_1$, $R_2$, $R_3$ maybe identical or different, wherein the individual groups $R_1$, $R_2$, $R_3$ themselves are structurally unitarily defined. This is characteristic for synthetic or semi-synthetic triglycerides. $R_1$, $R_2$, $R_3$ may however also consist of vari-

ous acyl groups of various structures. This is characteristic for triglycerides of a natural origin.

A triglyceride of the formula II is a semi-synthetic or synthetic, essentially pure triglyceride or a pharmaceutically used triglyceride of a natural origin. Preferred is a triglyceride of a natural origin, e.g. peanut oil, sesame oil, sunflower oil, olive oil, maize oil, soya oil, castor oil, cotton seed oil, rape oil, thistle oil, grape core oil, fish oil or coconut oil. In a particularly preferred embodiment form of the invention one uses a triglyceride with the term neutral oil with various acyl groups of a different structure, e.g. a triglyceride of the fractioned coconut fatty acids $C_8$-$C_{10}$ of the type Miglyol®, e.g. MIGLYOL 812.

The triglyceride (II) is, in the composition defined further above, contained in a preferred concentration range of approx. 0.1 to 2.0% by weight, preferably 0.1 to 1.0% by weight with respect to the total weight of the formulation.

The component e) - water as a carrier fluid in the purity required for the dermal application, is according to regulations of the national pharmaceutical list, free of germs and pyrogens.

The component f) - aiding agents suitable for dermal application is contained as a facultative component. Such aiding agents are contained in creams, ointments, gels, lotions, pastes, foams, tinctures or lotions.

Suitable are in particular ethanol, in particular in low quantity parts of approx 0.1 to 5%, isopropanol, further preservatives, e.g. benzalconium chloride, phenoxyethanol, further benzoe acids or their salts, 4-hydroxy-benzoe acid esters (PHB-esters), phenols, e.g. tert.-butyl-4-methoxy- or di-tert.-butyl-4-methylphenol, benzylalcohol, 4-chlor- or 2,4-dichlorbenzylalcohol, 2-phenylethanol, chlorhexidindi acetate or digluconate, thiabendazol, cetyltriammonium bromide, cetylpyridinium bromide, phenododecinium bromide or sorbic acid, antioxidants, e.g. ascorbic acid, cysteine, sulphites, e.g. sodium bisulphite, thioglycol or glutathion, essential oils for improving the smell, i.e. menthol oil, orange oil, bitter orange oil, mandarin oil or lemon oil, or solvents or means for preventing evaporation, e.g. polyalcohols, e.g. propylene glycol, polyethylene glycol or glycerine.

Likewise the subject-matter of the present invention is the method, known per se, for manufacturing the pharmaceutical composition, which is characterised in that one mixes a lipophile phase consisting of the components a) to d) with the aqueous carrier fluid which where

appropriate contains aiding agents suitable for dermal forms of administration, and where desired subjects the obtainable clear opalescent dispersion based on nanoparticles - nanodispersion - to the following subsequent operations: the addition of a further quantity of water as a carrier fluid as well as where appropriate further water soluble aiding agents, which are suitable for dermal forms of administration, and where appropriate filtration (e.g. sterile filtration) of the nanodispersion; and/or further processing of the nanodispersion to a dermal preparation.

According to this method one manufactures a lipophile phase "oil phase" consisting of the component c) - phospholipid (I) -, ethanol, component b) - partial fatty acid ester of polyoxyethylene sorbitan -, component a) - active ingredient, and of the component d) - triglyceride (II). The mixing of the components is effected at room temperature at low speed with a conventional stirrer with a propeller or winged blade, a magnet stirrer or static mixer.

In a preferred embodiment form of the invention one uses a combination of various partial fatty acid esters of polyoxyethylene sorbitan, in particular the combination consisting of polysorbate 20, 80 and 60. At the same time one respects the sequence, in that one first mixes the phospholipid and the ethanol together and then adds after one another polysorbate 20, 80, 60.

Subsequently one adds neutral oil. By mixing the lipophile phase ("oil phase") with the aqueous phase, which may contain water soluble facultative additions, e.g. preservatives, with a low speed mixing machinery (200 to 1,000 r.p.m.) there forms the pharmaceutical composition defined earlier, which may be defined as a dispersion of colloidal nanoparticles of the lipophile active ingredient hydrocortisone or simplified as a nanodispersion. On account of laser light dispersion measurements and recordings in the electron microscope the colloidal particles, present in the nanodispersion, of other formations such as fluid crystals, micelles, reverse micelles or liposomes may be distinguished. For the statistical majority of more than 95%, preferably more than 98% an average particle size of less than 50nm is characteristic.

For characterising the obtainable nanodispersion, methods known per se are suitable, e.g. optical judgement: weak to strong opalescence of the preparation can be easily recognised (indication of an average particle size of smaller than 50 nm), laser light dispersion (determining the particle size and homogeneity), electron microscopy (freezing breakage and negative contrast technology).

The nanodispersion is after the addition of the desired quantity of water and where appropriate further aiding agents, applicable for dermal forms of administra-

tion, e.g. directly applicable as a dosage spray. A particular advantage with respect to conventional dermal preparations is the possibility of sterile filtration. If desired by way of sterile filtration one may separate all larger particles with a diameter larger than approx. 200 nm in the dispersion, as well as floating and solid matter, and thus manufacture a nanodispersion with a fraction of particles with a relative uniform size.

Measured quantities of nanodispersion are filled, where appropriate as a concentrate, in suitable containers for a dose unit. Suitable vessels are e.g. vessels for pump sprays or dosage sprays or plastic vessels with an outlet device.

The pharmaceutical composition described earlier with the anti-inflammatory agent hydrocortisone is suitable as a dermal preparation for treating many diseases of the skin or on the eye. At the same time one applies the preparation in the prescribed dosage.

The following example illustrates the invention:

Recipe for a hydrocortisone 0.1% - nano-colloidal dosage spray formulation.

| position | dosage %(w/w) | amount g | component |
|---|---|---|---|
| 1 | 0.063 | 7.56 | Lipoid S100 |
| 2 | 0.625 | 75.00 | Ethanol abs. |
| 3 | 1.750 | 210.00 | Polysorbate 20 |
| 4 | 1.000 | 120.00 | Polysorbate 80 |
| 5 | 0.175 | 21.00 | Polysorbate 60 |
| 6 | 0.105 | 12.60 | hydrocortisone Base micro BP88 |
| 7 | 0.750 | 90.00 | Miglyol 812 |
| 8 | 94.930 | 11391.60 | Aqua purificata |
| 9 | 0.602 | 72.24 | phenoxyethanol |
| Total | 100.00 | 12000.00 | |

By the addition of (9) into (8) at room temperature one manufactures the aqueous phase. One obtains the oil phase by placing (1) into (2) until the solution becomes clear. Subsequently one adds after one another (3), (4), and (5) - polysorbate 20, 80 and 60 and stirs, until the mixture becomes clear. One adds the active ingredient (6) in three portions, and heats to 60° C until crystals are no longer visible. One adds (7) mixes until the solution becomes clear and cools to room temperature.

One unifies the aqueous phase with the oil phase, in that one places the aqueous phase at room temperature and stirs at 300 - 400 r.p.m with a magnetic stirring machinery. Subsequently one injects over a period of time of approx. two minutes slowly under the level the oil phase into the aqueous phase. One stirs for a further 5 - 10 minutes avoiding foam formation and filters the nanodispersion through a germ filter (0.2$\mu$m).

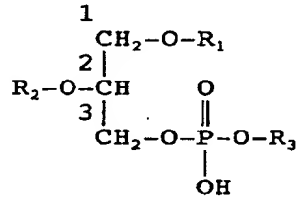
Claims

1. A pharmaceutical composition for the dermal application of a corticoid containing:

a) the active ingredient 11, 17, 21 -trihydroxypregn-4-en-3,20-dion (hydrocortisone) or a derivative thereof, where appropriate in combination with a wound healing agent;

b) at least one partial fatty acid ester of polyoxyethylene sorbitan or a combination thereof;

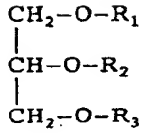
c) at least one essentially pure phospholipid of the formula:



(I)

where $R_1$ indicates $C_{10-20}$-acyl, $R_2$ hydrogen or $C_{10-20}$-acyl, $R_3$ hydrogen, 2-trimethylamino-1-ethyl, 2-amino-1-ethyl, $C_{1-4}$-alkyl, $C_{1-5}$-alkyl substituted by carboxy, $C_{2-5}$-alkyl substituted by hydroxy, $C_{2-5}$-alkyl substituted by carboxy and hydroxy or $C_{2-5}$-alkyl substituted by carboxy and amino, the inositol or glyceryl group, or salts of these compounds;

d) a triglyceride of the formula:



(II)

where $R_1$, $R_2$ and $R_3$ indicates $C_{8-24}$-acyl;

e) water as a carrier fluid in the purity required for the transdermal application; and where appropriate

f) aiding agents suitable for dermal forms of administration.

2. A pharmaceutical composition according to claim 1, containing as component a) the active ingredient hydrocortisone or the 21-acetate, 21-acetate-17-propionate (aceponate), 21-bendazac, 17α-butyrate, 17α-butyrate-21-propionate, 21-cipionate (cyclopentane propionate), 21-disodium phosphate, 21-hydrogen succinate, 21-sodium succinate, 21-tebutate (tert. butyl acetate), 17-valerate or xanthogenate, where appropriate in combination with an epithelisation agent.

3. A pharmaceutical composition according to claim 2 containing as a component a) the active ingredient hydrocortisone or the 21-acetate, where appropriate in combination with dexpanthenol.

4. A pharmaceutical composition according to one of claims 1 to 3 containing as component b) a combination of various partial fatty acid esters of polyoxyethylene sorbitan.

5. A pharmaceutical composition according to claim 4 containing as component b) the combination consisting of polysorbate 20, 80, 60.

6. A pharmaceutical composition according to one of the claims 1-5 containing as component c) purified lecithin of soya beans and as component d) a triglycerid from the group of neutral oils.

7. A pharmaceutical composition according to one of the claims 1-6 containing
a) the active ingredient hydrocortisone as a free base or the 21-acetate, where appropriate in combination with dexpanthenol;
b) the composition consisting of polysorbate 20, 80 and 60;
c) purified lecithin from soya beans;
d) a triglyceride from the group of neutral oils; and
e) water as a carrier fluid in the purity required for the dermal application; and where appropriate
f) aiding agents suitable for dermal forms of administration.

8. A method for manufacturing the pharmaceutical composition according to claim 1 for the dermal application of a corticoid, characterised in that one mixes a lipophile phase consisting of the components a) to d) with the aqueous carrier fluid which where appropriate contains aiding agents suitable for dermal forms of administration, and where desired subjects the obtainable clear opalescent dispersion based on nanoparticles - nanodispersion - to the following subsequent operations: the addition of a further quantity of water as a carrier fluid as well as where appropriate further water soluble aiding agents, which are suitable for dermal forms of administration, and where appropriate filtration of the nanodispersion; and/or further processing of the nanodispersion to a dermal preparation.

9. A method according to claim 8, characterised in that as component b) one uses the combination consisting of polysorbate 20, 80 and 60.

10. A method according to claim 9, characterised in that one adds polysorbate 20, polysorbate 80 and polysorbate 60 after one another.

11. The dispersion based on nanoparticles obtainable according to the method according to claim 7

12. The concentrate, filtrate or dry preparation containing nanoparticles with the active ingredient hydrocortisone, obtainable according to the method according to claim 7.

Cortisol spray

Abstract

The present invention relates to a pharmaceutical composition for the dermal application of hydrocortisone. One disperses this active ingredient with the addition of a partial fatty acid ester of polyoxyethylene sorbitan and of further aiding agents such as lecithin and neutral oil. With this one obtains a suspension of nanoparticles of the lipophile active ingredient hydrocortisone.